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REMARKS

The present application was originally filed with 19 Claims. In a Restriction Requirement mailed July 1, 2003, the Examiner restricted the Claims into four Groups, with Claims 1-12, drawn to a method of producing a transformed microorganism in Group I; Claim 13, drawn to a library of mutants in Group II; Claims 14-17, drawn to directed evolution of a host cell chromosome in Group III; and Claims 18 and 19, drawn to a method for constructing a sequence of interest in Group 4. In a Response filed August 22, 2003, Applicants elected the Claims in Group I (Claims 1-12), and the species *Bacillus*, with the request that the remaining species be examined, upon the determination that the species *Bacillus* is patentable. Applicants have cancelled Claims 13-19, as well as Claims 2, 3 and 8 without prejudice and reserve the right to pursue these Claims and/or similar Claims in one or more Divisional or other applications.

Applicants note that the Examiner has indicated that one reference included in the Information Disclosure Statement (IDS) has not been considered. This reference is cited in the application as filed and is simply a dictionary with definitions specifically pertaining to biology. Applicants further note that the Examiner has objected to the form of Claim 12. This Claim has been amended to make it more clear. There is no need for antecedent basis for this element, as it is a new element added in this dependent Claim.

The Examiner's rejections are addressed in the following order:

- 1) Claims 1-12 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
- 2) Claims 1-12 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly not meeting the written description requirement; and
- 3) Claims 1-12 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated.

1) The Claims are Definite

The Examiner has rejected Claims 1-12 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner argues that the Claims are indefinite for the recitation of the term "selecting." Although Applicants believe that the Claims were definite as filed and the language was intended to recite a competent microorganism from any source,

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Applicants have amended Claim 1 without prejudice to recite "providing a competent microorganism"

The Examiner has rejected Claim 12 as allegedly being indefinite for the recitation of "increasing" the homology between the target sequence and the DNA construct. The Examiner argues that the term is a relative term that renders the Claim indefinite and that the term is not defined by the Claim. Applicants must respectfully disagree as the plain meaning of "increasing" is known in the art and the embodiment involving an increase in homology is described in the present Specification as filed (See e.g., Example 5). Nonetheless, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended Claim 1 to recite the presence of an incoming sequence of interest flanked by homology boxes. Claim 12 has also been amended to recite that there is an increase in the sequence homology between at least one of the homology boxes and the target sequence. Furthermore, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended the Claims to recite a DNA construct that comprises an incoming sequence of interest, flanked on each side by a homology box, wherein the homology boxes are flanked by non-heterologous sequences which are non-critical targets for the microorganism to initiate uptake of the DNA construct. Support for this amendment is provided by the Specification as filed (See e.g., page 7 line 13 through page 8, line 9; page 9, lines 21-26, page 12, lines 13-27; page 4, lines 23-25; and Figure 2). Thus, no new matter is added by these amendments. Applicants have amended the Claims without prejudice and reserve the right to prosecute the original Claims (and/or other similar Claims) in additional applications. As the pending Claims are definite, Applicants respectfully request that this rejection be withdrawn.

2) The Claims Meet the Written Description Requirement

The Examiner has rejected Claims 1-12 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly not meeting the written description requirement. In particular, the Examiner argues that ". . . the Specification and claims do not provide any guidance as to what structural features all of the claimed variants might share" (emphasis original) (Office Action, page 6). Applicants must respectfully disagree. Nonetheless, in order to further their business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended the Claims to recite that the microorganism is

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Bacillus, and that the DNA construct comprises an incoming sequence flanked by homology boxes, as well as further flanking non-homologous sequences which serve as non-critical targets for initiation of uptake of the DNA construct. Thus, it is clear that the claimed method requires the use of *Bacillus* as the microorganism to be transformed and that the DNA construct be comprised of an incoming sequence of interest flanked by homology boxes and further flanked by non-homologous regions that serve to initiate the uptake of the construct. Thus, the present Claims provide the structure required. As filed, the Specification and Claims describe the claimed methods of the present invention. Thus, Applicants respectfully request that this rejection be withdrawn.

3) The Claims Are Novel

Claims 1-12 stand rejected under 35 U.S.C. §102(b), as allegedly being anticipated. In particular, the Examiner argues that Claims 1-12 are allegedly anticipated by Hahn *et al.*; Claims 1-3 and 6-9 are allegedly anticipated by Niaudet *et al.*; Claims 1-4, 5-7, 10 and 11 are allegedly anticipated by van Sinderen and Venema *et al.*; Claims 1-3, 6, 7, 10, and 11 are allegedly anticipated by U.S. Patent No. 4,828,994; and Claims 1-3, 6 and 7 are allegedly anticipated by EP 0761815. Applicants must respectfully disagree. In order for a reference to anticipate a Claim, each and every element of the Claim must be disclosed in the reference². Applicants respectfully submit that none of the references cited by the Examiner against the present Claims meets this requirement.

A. Claims 1-12 are Novel Over the Hahn *et al.* Reference

The Examiner argues that "Hahn teaches a method of producing a transformed microorganism comprising the direct introduction and subsequent chromosomal integration of a DNA construct produced in vitro into a selected competent microorganism" (Office Action, page 11). Applicants must respectfully disagree, as it appears that the strains described by Hahn *et al.* were all produced using plasmids, as indicated on pages 772-773 of Hahn *et al.* Furthermore, contrary to the Examiner's statements, shuttle vectors were used in the Hahn *et al.* work, as indicated on page 772, in the description of the construction of a multicopy comS

² Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention." (*RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984)).

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plasmid. As the Hahn *et al.* reference fails to disclose the direct transformation of a microorganism without the use of a plasmid, shuttle vector, and there is no mention of increasing the homology between the target sequence and the construct (the passage in the Hahn *et al.* reference cited by the Examiner does not provide any indication that the homology between the target and construct was increased, as set forth in the present Specification), Applicants respectfully submit that the Hahn *et al.* reference does not anticipate the presently claimed invention.

However, as indicated above, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended the Claims to recite a DNA construct that comprises an incoming sequence of interest, flanked on each side by a homology box, wherein the homology boxes are flanked by non-heterologous sequences which are non-critical targets for the microorganism to initiate uptake of the DNA construct. Support for this amendment is provided by the Specification as filed (See e.g., page 7 line 13 through page 8, line 9; page 9, lines 21-26, page 12, lines 13-27; page 4, lines 23-25; and Figure 2). Thus, no new matter is added by these amendments.

B. Claims 1-3 and 6-9 are Novel Over Niaudet *et al.*

With regard to Niaudet *et al.*, the Examiner argues that this reference teaches selecting a competent microorganism (*Bacillus*), producing a DNA construct having stuffer sequences and homologous and heterologous sequences, and directly transforming the microorganism with the DNA such that it becomes integrated. Applicants must respectfully disagree and submit that the Niaudet *et al.* reference does not anticipate the presently claimed invention. The Niaudet *et al.* reference describes the chromosomal integration of DNA molecules that have regions of homology with the chromosome. Unlike the presently claimed invention, these homologous regions (*i.e.*, homology boxes) are not flanked by non-homologous regions that are non-critical targets for the microorganism to initiate uptake of the DNA construct. As this reference fails to disclose each and every element of the presently claimed invention, Applicants respectfully submit that this reference does not anticipate the Claims and request that this rejection be withdrawn.

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C. Claims 1-4, 5-7, 10 and 11 are Novel Over van Sinderen and V nema et al

With regard to this reference, the Examiner argues that this reference teaches the direct introduction and subsequent chromosomal integration of a DNA construct comprising homologous and heterologous sequences. The Examiner further argues that the reference teaches a method of producing a transformed organism comprising the direct introduction and subsequent chromosomal integration of a DNA construct that was not produced with the use of a shuttle vector nor an intermediate host. However, unlike the presently claimed invention, the homologous regions (*i.e.*, homology boxes) are not flanked by non-homologous regions that are non-critical targets for the microorganism to initiate uptake of the DNA construct. As this reference fails to disclose each and every element of the presently claimed invention, Applicants respectfully submit that this reference does not anticipate the Claims and request that this rejection be withdrawn.

D. Claims 1-3, 6, 7, 10, and 11 are Novel Over U.S. Patent No. 4,828,994

With regard to this reference, the Examiner argues that this Patent teaches a method of producing a transformed microorganism by direct transformation and subsequent chromosomal integration of a DNA construct having homologous and heterologous sequences. As with the other references, this Patent fails to disclose the elements recited in the amended Claims. Applicants respectfully request that this rejection be withdrawn.

E. Claims 1-3, 6 and 7 are Novel Over EP 0761815

With regard to this reference, the Examiner argues that it teaches a method of producing a transformed microorganism comprising the direct transformation and subsequent chromosomal integration of a DNA construct, wherein the construct comprises homologous and heterologous sequences. Applicants must respectfully disagree. Although there are homologous boxes in the present Claims, the present Claims also recite non-homologous regions that flank the homology boxes and serve as non-critical targets for integration. As this reference fails to disclose each and every element of the presently claimed invention, Applicants respectfully submit that this reference does not anticipate the Claims and request that this rejection be withdrawn.

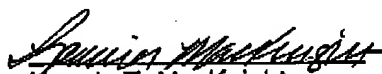
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CONCLUSION

All grounds of rejection and objection of the Office Action of October 20, 2003, having been addressed, reconsideration of the application is respectfully requested. Applicants respectfully submit that the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-5838.

Respectfully submitted,

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